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Risk Factors and Clinical Impact of *Klebsiella pneumoniae* Carbapenemase–Producing *K. pneumoniae*

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Abstract

BACKGROUND—*Klebsiella pneumoniae* carbapenemase (KPC)–producing *K. pneumoniae* is an emerging pathogen with serious clinical and infection control implications. To our knowledge, no study has specifically examined risk factors for KPC-producing *K. pneumoniae* or its impact on mortality.

METHODS—To identify risk factors for infection or colonization with KPC-producing *K. pneumoniae*, a case-control study was performed. Case patients with KPC-producing *K. pneumoniae* were compared with control subjects with carbapenem-susceptible *K. pneumoniae.* A cohort study evaluated the association between KPC-producing *K. pneumoniae* and in-hospital mortality.

RESULTS—Fifty-six case patients and 863 control subjects were identified. In multivariable analysis, independent risk factors for KPC-producing *K. pneumoniae* were (1) severe illness (adjusted odds ratio [AOR], 4.31; 95% confidence interval [CI], 2.25–8.25), (2) prior fluoroquinolone use (AOR, 3.39; 95% CI, 1.50, 7.66), and (3) prior extended-spectrum cephalosporin use (AOR, 2.55; 95% CI, 1.18, 5.52). Compared with samples from other anatomic locations, *K. pneumoniae* isolates from blood samples were less likely to harbor KPC (AOR, 0.33; 95% CI, 0.12, 0.86). KPC-producing *K. pneumoniae* was independently associated with in-hospital mortality (AOR, 3.60; 95% CI, 1.87–6.91).

CONCLUSIONS—KPC-producing *K. pneumoniae* is an emerging pathogen associated with significant mortality. Our findings highlight the urgent need to develop strategies for prevention and infection control. Limiting use of certain antimicrobials, specifically fluoroquinolones and cephalosporins, use may be effective strategies.

In North America, *Klebsiella* species are among the most common pathogens recovered in intensive care units.[1,2] *Klebsiella pneumoniae* is also among the bacteria that most readily develop resistance mechanisms to multiple classes of antibiotics, and the prevalence of drug

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resistance is increasing at an alarming rate.[3,4] Because of the emergence of extended-spectrum *β*-lactamases, carbapenems have been the agents of choice for the management of multidrug-resistant *K. pneumoniae* infection.

Carbapenem resistance among *K. pneumoniae* emerged a decade ago.[5] Reports of carbapenem resistance were initially sporadic, and such resistance was attributed to several mechanisms, including high-level production of an AmpC *β*-lactamase combined with loss of outer membrane proteins or, rarely, efficient carbapenem-hydrolyzing *β*-lactamases (eg, the class B metallo-*β*-lactamases).[6] However, in 2001, a plasmid-mediated class A *β*-lactamase enzyme, *K. pneumoniae* carbapenemase type 1 (KPC-1), was identified in *K. pneumoniae.* Initially limited to the northeastern United States, where the prevalence of the KPC enzyme among *K. pneumoniae* is as high as 24% in some areas, KPC-type enzymes (ie, KPC-2 and KPC-3) have spread globally at an alarming rate.[7–11] KPC production may be an even greater problem than currently recognized, because carbapenem resistance in KPC-producing *K. pneumoniae* isolates is frequently not detected by automated microdilution susceptibility testing routinely used in clinical microbiology laboratories.[8,12] In most cases, because of the existence of multiple resistance mechanisms associated with KPC-containing plasmids, few therapeutic options exist for treating infections due to KPC-producing *K. pneumoniae,* and high mortality has been reported.[8,13,14]

KPC-producing *K. pneumoniae* appears to be the next major challenge in antimicrobial resistance. Closer investigation of the risk factors and impact of this organism is warranted to develop interventions aimed at curbing its rapid emergence. Although risk factors for carbapenem-resistant *K. pneumoniae* have been reported by several investigators,[14–17] we are unaware of any study that has investigated risk factors for carbapenem resistance specifically caused by the presence of KPC. As such, this study aims to identify risk factors for isolation of KPC-producing *K. pneumoniae* in clinical cultures among a large cohort of patients. We also assessed the independent impact of KPC-producing *K. pneumoniae* on mortality.

METHODS

This study was conducted at the Hospital of the University of Pennsylvania (Philadelphia), a 725-bed academic tertiary care medical center, and Penn Presbyterian Medical Center (Philadelphia), a 344-bed urban hospital. The study was approved by the Committee on Studies Involving Human Beings of the University of Pennsylvania.

A case-control study was performed to identify risk factors for KPC-producing *K. pneumoniae.* All patients older than 18 years who had an inpatient clinical culture positive for *K. pneumoniae* from October 1, 2006 through April 30, 2008, were eligible for inclusion. Individuals became eligible on the first day that a *K. pneumoniae* isolate was identified, and each individual was eligible only once, regardless of whether *K. pneumoniae* was isolated on subsequent days. Patients with KPC-producing *K. pneumoniae* were designated as case patients. To evaluate for the presence of KPC, *K. pneumoniae* isolates were screened for carbapenem nonsusceptibility with use of ertapenem by disk diffusion testing or by Vitek2 panel GN-20 (bioMérieux).[18] Ertapenem has been shown to be more sensitive in identifying carbapenem resistance, compared with imipenem and meropenem.[8,19] KPC-producing *K. pneumoniae* was then confirmed using either polymerase chain reaction (PCR) to detect bla_{KPC} or the Modified Hodge test phenotypic assay using meropenem as the indicator.[20] In the United States, where carbapenemases in *K. pneumoniae* are almost exclusively attributable to KPC, the Modified Hodge test has shown 100% specificity and sensitivity in published reports[20] and in testing at our institution. All carbapenem-nonsusceptible isolates with negative PCR and/or phenotypic testing results were excluded. The mechanism of carbapenem

nonsusceptibility in these isolates was presumed to be a porin mutation plus an extended-spectrum β-lactamase and/or AmpC, rather than KPC production.

All patients with carbapenem-susceptible *K. pneumoniae* yielded by an inpatient clinical culture during the study period were designated as control subjects. Although there has been considerable debate regarding the choice of control groups in studies of antimicrobial resistance, we chose persons with carbapenem-susceptible *K. pneumoniae* to be our control subjects, because we sought specifically to evaluate risk factors for KPC production among patients with *K. pneumoniae* infection or colonization.[21]

Potential risk factors were assessed through the use of a comprehensive health system computer database, which has been used effectively for similar studies of antimicrobial use in the past.[22] Data obtained included age, sex, race, origin of patient at the time of hospital admission (eg, home or transferred from another institution), hospital location at the time that the clinical isolate was identified, and duration of hospital stay prior to identification of the isolate. The anatomic source of the *K. pneumoniae* isolate and the antibiotic susceptibility profile of the isolate were noted. If *K. pneumoniae* was identified in more than 1 anatomic site on the same day, other sites were noted. Nosocomial acquisition was defined as an isolate identified more than 48 hours after admission to the hospital or an isolate identified no later than 48 hours after admission in a patient transferred from another medical institution (eg, other hospital or long-term care facility). Prior antibiotic exposure was defined as at least 2 days of therapy administered during the 30 days prior to the culture. The presence of comorbid conditions was documented; such conditions included hepatic dysfunction and/or cirrhosis, anemia (indicated by hemoglobin level less than 10.0 g/dL), malignancy, diabetes mellitus, renal insufficiency (indicated by creatinine level >2.0 mg/dL or the requirement of dialysis), human immunodeficiency virus (HIV) infection, cardiopulmonary disease, and a history of solid organ transplantation. To adjust for severity of illness, we used the All Patient Refined Diagnosis Related Group (APR-DRG) method to classify patients into 4 severity of illness categories: minor, moderate, major, and extreme.[23]

Bivariable analyses were conducted to determine the unadjusted association between potential risk factors and the presence of KPC-producing *K. pneumoniae.* Categorical variables were compared using the Fisher exact test. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated to evaluate the strength of any association. Continuous variables were compared using the Student *t* test or the Wilcoxon rank-sum test, depending on the validity of the normality assumption. Multivariable analysis was performed using forward stepwise multiple logistic regression. Variables with a P value <.20 in bivariable analyses were considered for inclusion in a multivariable model. Backward stepwise multiple logistic regression was also performed to determine whether identification of risk factors varied with the approach to multivariable analysis.

A cohort study was performed to evaluate the association between isolation of a KPC-producing *K. pneumoniae* isolate and in-hospital mortality. Individuals previously identified as case patients and control subjects comprised the exposed (patients with KPC-producing *K. pneumoniae* infection) and unexposed (patients with carbapenem-susceptible *K. pneumoniae* infection) participants in the cohort study, respectively. Bivariable analyses were performed, and variables with $P < .2$ in bivariable analysis were considered for inclusion in a multivariable model. Variables remained in the final model if their inclusion resulted in a >15% change in the effect size for the association between isolation of KPC-producing *K. pneumoniae* and mortality.

For all calculations, a 2-tailed P value <.05 was considered to be statistically significant. All statistical calculations were performed using standard programs in Stata, version 10.0 (Stata).

RESULTS

During the study period, 928 inpatients had a clinical culture positive for *K. pneumoniae.* Carbapenem-resistant *K. pneumoniae* was identified in 65 individuals, and KPC-producing *K. pneumoniae* was confirmed in 56. Carbapenem resistance was attributable to alternative mechanisms in 6 isolates, and 3 isolates were not available for PCR and/or Modified Hodge testing; individuals with these isolates were excluded. Anatomic sites of cultures were urine in 550 individuals (59.9%), blood in 162 (17.3%), respiratory tract in 111 (12.1%), abdomen in 81 (8.1%), and other or unknown in 61 (6.6%). Of note, *K. pneumoniae* was simultaneously identified in multiple sites in 41 individuals, including blood and urine in 30 and blood and abdomen in 5.

Case patients were more often critically ill, as indicated by a higher rate of intensive care unit admission, the use of mechanical ventilation, and categorization of illness as extreme by APR-DRG (Table 1). Prior use of numerous antibiotics was also significantly more common among case patients. There were no differences in age or race, aminoglycoside use, and the presence of comorbidities (ie, malignancy, liver disease, renal insufficiency, cardiopulmonary disease, HIV infection, diabetes, and history of solid organ transplantation). In multivariable analysis (Table 2), APR-DRG extreme illness category, prior fluoroquinolone use, and prior extended-spectrum cephalosporin use were significantly associated with isolation of KPC-producing *K. pneumoniae.* Isolates obtained from the blood were less likely to harbor KPC, compared with those obtained from other anatomic sites. Results of backward and forward stepwise regression were not substantively different.

Among the 56 persons who had KPC-producing *K. pneumoniae* isolated, 18 (32.1%) died during hospitalization, compared with 85 (9.9%) of the 863 patients who had carbapenem-susceptible *K. pneumoniae* isolated ($P < .001$). Among patients who died, time to death after the date of the first positive culture result was significantly longer for patients with KPC-producing *K. pneumoniae* than for patients with carbapenem-susceptible *K. pneumoniae.* The median period from the first positive *K. pneumoniae* culture result to death was 18 days (interquartile range, 5–23 days) among patients with KPC-producing *K. pneumoniae* infection, compared with 8 days (interquartile range, 3–16 days) among patients with carbapenem-susceptible *K. pneumoniae* infection ($P = .02$). In a multivariable model, APR-DRG extreme severity of illness and use of mechanical ventilation on the day of culture confounded the relationship with isolation of KPC-producing *K. pneumoniae;* however, infection or colonization with KPC-producing *K. pneumoniae* remained significantly associated with in-hospital mortality (adjusted OR, 2.28; 95% CI, 1.18–4.40; $P < .02$).

DISCUSSION

Our study demonstrates that severity of illness, prior fluoroquinolone use, and prior extended-spectrum cephalosporin use are risk factors for isolation of KPC-producing *K. pneumoniae.* We also found that isolation of KPC-producing *K. pneumoniae* is independently associated with in-hospital mortality.

There is ample laboratory evidence to support an association between KPC and prior fluoroquinolone use. Plasmid-encoded *qnr* genes, which convey low-level fluoroquinolone resistance, have been identified in the same conjugative *K. pneumoniae* plasmid as KPC genes (specifically $bla_{\text{kpc-2}}$ and *qnr*B4).[24] Similarly, Endimiani et al identified both $bla_{\text{kpc-3}}$ and *qnr*B19 on the transferable *K. pneumoniae* plasmid pLRM24.[25] Those authors subsequently identified a complex genetic region, the KQ element (KPC and *qnr*), which not only contains $bla_{\text{kpc-3}}$ and *qnr*B19 but also is associated with a Tn*4401*-like element.[26] Previous work suggested that the putative KPC-2 encoding transposon Tn*4401* contributes to the

dissemination of these enzymes.[27] Indeed, fluoroquinolone use has been identified as a risk factor for carbapenem-resistant *K. pneumoniae* infection in past epidemiologic studies, although those studies did not focus specifically on carbapenem resistance due to KPC production.[14,15]

That yet another resistance pattern appears to be associated with fluoroquinolone use is concerning, especially in light of widespread prescribing of these drugs in recent years.[28] Fluoroquinolone use has been associated with the emergence of resistance to other nonfluoroquinolone agents and multidrug resistance in a variety of bacteria.[22,29–32] Not surprisingly, plasmids carrying *qnr* usually also encode other non-KPC resistance genes, particularly extended-spectrum *β*-lactamases.[33]

Prior cephalosporin use[16,17] and prior carbapenem use[14,16,17] have been associated with carbapenem-resistant *K. pneumoniae* in previous studies. In our study, very few patients had a history of carbapenem use (1.1%). As such, prior use of carbapenems as a risk factor for KPC production in *K. pneumoniae* isolates cannot be excluded. However, KPC enzymes have been shown to confer greater resistance to cephalosporins than to carbapenems, and therefore, a significant selective pressure for KPC-harboring bacteria induced by cephalosporin use is certainly plausible.[34] Because existing studies included all carbapenem-resistant *K. pneumoniae* isolates, regardless of mechanism of resistance, future studies should better clarify the role of carbapenem use in the acquisition of KPC-producing *K. pneumoniae.*

In the present cohort study, we confirmed that identification of a KPC-producing *K. pneumoniae* isolate is associated with in-hospital mortality. We also found that death was delayed among case patients, compared with control subjects. Although these findings are interesting, several limitations of our study warrant future studies to more closely examine factors associated with mortality to better elucidate the clinical course of infection due to KPC-producing *K. pneumoniae.* Although we controlled for severity of illness, we were not able to differentiate between infection and colonization, and the high in-hospital mortality may reflect the severity of underlying disease rather than infection with KPC-producing *K. pneumoniae.* Of note, because we did not follow up with patients after the hospital admission during which their first *K. pneumoniae* isolate was identified, the impact on mortality may also be underestimated. We did not evaluate choice of therapy or time to appropriate therapy. In a prior study, only failure to remove the source of infection, not time to therapy, was associated with mortality among patients with infection due to carbapenem-resistant *K. pneumoniae.*[17] In this study, however, no adjustment was made for severity of illness, and these findings may not hold true for carbapenem resistance due to KPC-producing *K. pneumoniae.*

Our study is unique in several ways. There have been few studies examining carbapenem resistance among *K. pneumoniae,* but none specifically examined risk factors for KPC production as confirmed by PCR and/or Modified Hodge testing.[14–17,35] Several of these studies were performed before the documentation of KPC in the geographic area of the study setting.[15,16,35] Furthermore, many used automated carbapenem testing, which does not detect carbapenem resistance in 6%–87% of known resistant isolates.[12] Finally, no study used ertapenem to screen for carbapanem resistance; ertapenem has been shown to be a more sensitive indicator of KPC than meropenem and imipenem.[12,20] Although carbapenem-resistant isolates may be phenotypically similar, risk factors and outcomes may differ according to the mechanism of resistance.

Several additional potential limitations exist. We did not include details regarding prior antibiotic exposure in an out-patient context, because these data were not consistently available. Our study was conducted in a large tertiary care medical center, and the results may not be generalizable to other institutions. Of interest, time to identification of KPC-producing *K.*

pneumoniae was relatively short in our study, compared with others (4 days). This may reflect differences in patient population and/or transmission dynamics at our institution. Although we attempted to control for potential confounders, residual confounding by unknown or unmeasured confounders is possible in any nonrandomized study. As mentioned, we did not determine whether a positive clinical culture represented colonization or infection and used only clinical cultures, rather than performing surveillance, to detect colonization with KPC-producing bacteria. Of note, the optimal method for detecting asymptomatic patients colonized with KPC-producing *K. pneumoniae* is still unknown.

KPC-producing *K. pneumoniae* is an emerging pathogen associated with significant mortality. Our current antimicrobial armamentarium is ill equipped to battle infections caused by this organism. Our findings highlight the urgent need to develop strategies for prevention and infection control and underscore the importance of using antimicrobial stewardship to minimize unnecessary and inappropriate antimicrobial use, particularly of fluoroquinolones and extended-spectrum cephalosporins. Restriction of fluoroquinolone use appears to be particularly important in the fight against the emergence of antimicrobial resistance.

References

1. Neuhauser MM, Weinstein RA, Rydman R, Danziger LH, Karam G, Quinn JP. Antibiotic resistance among gram-negative bacilli in US intensive care units: implications for fluoroquinolone use. JAMA 2003;289:885–888. [PubMed: 12588273]
2. Streit JM, Jones RN, Sader HS, Fritsche TR. Assessment of pathogen occurrences and resistance profiles among infected patients in the intensive care unit: report from the SENTRY Antimicrobial Surveillance Program (North America, 2001). Int J Antimicrob Agents 2004;24:111–118. [PubMed: 15288308]
3. Falagas ME, Bliziotis IA. Pandrug-resistant gram-negative bacteria: the dawn of the post-antibiotic era? Int J Antimicrob Agents 2007;29:630–636. [PubMed: 17306965]
4. National Nosocomial Infections Surveillance S. National Nosocomial Infections Surveillance (NNIS) System Report, data summary from January 1992 through June 2004, issued October 2004. Am J Infect Control 2004;32:470–485. [PubMed: 15573054]
5. MacKenzie FM, Forbes KJ, Dorai-John T, Amyes SG, Gould IM. Emergence of a carbapenem-resistant *Klebsiella pneumoniae*. Lancet 1997;350:783. [PubMed: 9298003]
6. Bradford PA, Bratu S, Urban C, et al. Emergence of carbapenem-resistant *Klebsiella* species possessing the class A carbapenem-hydrolyzing KPC-2 and inhibitor-resistant TEM-30 beta-lactamases in New York City. Clin Infect Dis 2004;39:55–60. [PubMed: 15206053]
7. Leavitt A, Navon-Venezia S, Chmelnitsky I, Schwaber MJ, Carmeli Y. Emergence of KPC-2 and KPC-3 in carbapenem-resistant *Klebsiella pneumoniae* strains in an Israeli hospital. Antimicrob Agents Chemother 2007;51:3026–3029. [PubMed: 17562800]
8. Bratu S, Mooty M, Nichani S, et al. Emergence of KPC-possessing *Klebsiella pneumoniae* in Brooklyn, New York: epidemiology and recommendations for detection. Antimicrob Agents Chemother 2005;49:3018–3020. [PubMed: 15980389]
9. Pope J, Adams J, Doi Y, Szabo D, Paterson DL. KPC type beta-lactamase, rural Pennsylvania. Emerg Infect Dis 2006;12:1613–1614. [PubMed: 17176590]
10. Villegas MV, Lolans K, Correa A, et al. First detection of the plasmid-mediated class A carbapenemase KPC-2 in clinical isolates of *Klebsiella pneumoniae* from South America. Antimicrob Agents Chemother 2006;50:2880–2882. [PubMed: 16870793]
11. Zhang R, Zhou HW, Cai JC, Chen GX. Plasmid-mediated carbapenem-hydrolysing beta-lactamase KPC-2 in carbapenem-resistant *Serratia marcescens* isolates from Hangzhou, China. J Antimicrob Chemother 2007;59:574–576. [PubMed: 17251347]
12. Tenover FC, Kalsi RK, Williams PP, et al. Carbapenem resistance in *Klebsiella pneumoniae* not detected by automated susceptibility testing. Emerg Infect Dis 2006;12:1209–1213. [PubMed: 16965699]

13. Bratu S, Landman D, Haag R, et al. Rapid spread of carbapenem-resistant *Klebsiella pneumoniae* in New York City: a new threat to our antibiotic armamentarium. Arch Intern Med 2005;165:1430–1435. [PubMed: 15983294]
14. Schwaber MJ, Klarfeld-Lidji S, Navon-Venezia S, Schwartz D, Leavitt A, Carmeli Y. Predictors of carbapenem-resistant *Klebsiella pneumoniae* acquisition among hospitalized adults and effect of acquisition on mortality. Antimicrob Agents Chemother 2008;52:1028–1033. [PubMed: 18086836]
15. Falagas ME, Rafailidis PI, Kofteridis D, et al. Risk factors of carbapenem-resistant *Klebsiella pneumoniae* infections: a matched case control study. J Antimicrob Chemother 2007;60:1124–1130. [PubMed: 17884829]
16. Kwak YG, Choi SH, Choo EJ, et al. Risk factors for the acquisition of carbapenem-resistant *Klebsiella pneumoniae* among hospitalized patients. Microb Drug Resist 2005;11:165–169. [PubMed: 15910232]
17. Patel G, Huprikar S, Factor S, Jenkins S, Calfee D. Outcomes of carbapenem-resistant *Klebsiella pneumoniae* infection and the impact of antimicrobial and adjunctive therapies. Infect Control Hosp Epidemiol 2008;29:1099–1106. [PubMed: 18973455]
18. McGettigan SE, Adreaecchio K, Edelstein PH. Specificity of ertapenem susceptibility screening for the detection of *Klebsiella pneumoniae* carbapenemases (KPC). J Clin Microbiol 2009;47:785–786. [PubMed: 19144799]
19. Lomaestro BM, Tobin EH, Shang W, Gootz T. The spread of *Klebsiella pneumoniae* carbapenemase-producing *K. pneumoniae* to upstate New York. Clin Infect Dis 2006;43:e26–e28. [PubMed: 16804837]
20. Anderson KF, Lonsway DR, Rasheed JK, et al. Evaluation of methods to identify the *Klebsiella pneumoniae* carbapenemase in Enterobacteriaceae. J Clin Microbiol 2007;45:2723–2725. [PubMed: 17581941]
21. Harris AD, Karchmer TB, Carmeli Y, Samore MH. Methodological principles of case-control studies that analyzed risk factors for antibiotic resistance: a systematic review. Clin Infect Dis 2001;32:1055–1061. [PubMed: 11264034]
22. Gasink LB, Fishman NO, Nachamkin I, Bilker WB, Lautenbach E. Risk factors for and impact of infection or colonization with aztreonam-resistant *Pseudomonas aeruginosa*. Infect Control Hosp Epidemiol 2007;28:1175–1180. [PubMed: 17828695]
23. 3M Health Information Systems. All-patient refined diagnosis related groups (APR-DRGs) methodology overview, version 20. Wallingford, CT: 3M Health Information Systems; 2003.
24. Mendes RE, Bell JM, Turnidge JD, et al. Carbapenem-resistant isolates of *Klebsiella pneumoniae* in China and detection of a conjugative plasmid (blaKPC-2 plus qnrB4) and a blaIMP-4 gene. Antimicrob Agents Chemother 2008;52:798–799. [PubMed: 18086850]
25. Endimiani A, Carias LL, Hujer AM, et al. Presence of plasmid-mediated quinolone resistance in *Klebsiella pneumoniae* isolates possessing blaKPC in the United States. Antimicrob Agents Chemother 2008;52:2680–2682. [PubMed: 18426899]
26. Rice LB, Carias LL, Hutton RA, Rudin SD, Endimiani A, Bonomo RA. The KQ element, a complex genetic region conferring transferable resistance to carbapenems, aminoglycosides, and fluoroquinolones in *Klebsiella pneumoniae*. Antimicrob Agents Chemother 2008;52:3427–3429. [PubMed: 18573935]
27. Naas T, Cuzon G, Villegas MV, Lartigue MF, Quinn JP, Nordmann P. Genetic structures at the origin of acquisition of the beta-lactamase bla KPC gene. Antimicrob Agents Chemother 2008;52:1257–1263. [PubMed: 18227185]
28. Linder JA, Huang ES, Steinman MA, Gonzales R, Stafford RS. Fluoroquinolone prescribing in the United States: 1995 to 2002. Am J Med 2005;118:259–268. [PubMed: 15745724]
29. Gould CV, Fishman NO, Nachamkin I, Lautenbach E. Chloramphenicol resistance in vancomycin-resistant enterococcal bacteremia: impact of prior fluoroquinolone use? Infect Control Hosp Epidemiol 2004;25:138–145. [PubMed: 14994940]
30. Wiener J, Quinn JP, Bradford PA, et al. Multiple antibiotic-resistant *Klebsiella* and *Escherichia coli* in nursing homes. JAMA 1999;281:517–523. [PubMed: 10022107]

31. Lautenbach E, Weiner MG, Nachamkin I, Bilker WB, Sheridan A, Fish-man NO. Imipenem resistance among *Pseudomonas aeruginosa*: risk factors for emergence and impact of resistance on clinical and economic outcomes. Infect Control Hosp Epidemiol 2006;27:893–900. [PubMed: 16941312]

32. Paramythiotou E, Lucet JC, Timsit JF, et al. Acquisition of multidrug-resistant *Pseudomonas aeruginosa* in patients in intensive care units: role of antibiotics with antipseudomonal activity. Clin Infect Dis 2004;38:670–677. [PubMed: 14986251]

33. Jacoby GA. Mechanisms of resistance to quinolones. Clin Infect Dis 2005;41(Suppl 2):S120–S126. [PubMed: 15942878]

34. Woodford N, Tierno PM Jr, Young K, et al. Outbreak of *Klebsiella pneumoniae* producing a new carbapenem-hydrolyzing class A beta-lactamase, KPC-3, in a New York Medical Center. Antimicrob Agents Chemother 2004;48:4793–4799. [PubMed: 15561858]

35. Ahmad M, Urban C, Mariano N, et al. Clinical characteristics and molecular epidemiology associated with imipenem-resistant *Klebsiella pneumoniae*. Clin Infect Dis 1999;29:352–355. [PubMed: 10476741]

TABLE 1

Factors Associated with *Klebsiella pneumoniae* Carbapenemase–Producing *K. pneumoniae* in Bivariable Analysis

Variable	Case patients (*n* = 56)	Control subjects (*n* = 863)	OR (95% CI)	*P*[a]
Time from hospital admission to *K. pneumonia* isolation, median days (IQR)	4 (1–15)	1 (0–6)	…	.004
Transfer[b]	20 (35.7)	153 (17.7)	2.58 (1.37–4.72)	<.001
Female sex	28 (50.0)	354 (41.0)	1.44 (0.80–2.56)	.19
Used mechanical ventilation at time of isolate identification	17 (30.4)	126 (14.6)	2.55 (1.31–4.78)	.002
Surgical service	31 (55.4)	336 (38.9)	1.94 (1.09–3.50)	.02
Stayed in ICU at the time of culture	19 (33.9)	192 (22.3)	1.79 (0.95–3.29)	.04
APR-DRG severity of illness extreme	42 (75.0)	317 (36.7)	5.17 (2.71–10.40)	<.001
Prior antimicrobial use				
Fluoroquinolones	10 (17.9)	30 (3.5)	6.03 (2.47–13.62)	<.001
Carbapenems	2 (3.6)	8 (0.9)	3.96 (0.40–20.46)	.06
Extended-spectrum cephalosporins	11 (19.6)	46 (5.3)	4.34 (1.89–9.22)	<.001
First- or second-generation cephalosporins	5 (8.9)	35 (4.1)	2.32 (0.68–6.30)	.08
Piperacillin-tazobactam	6 (10.7)	31 (3.6)	3.22 (1.05–8.32)	.009
Anti-anaerobic drug[c]	20 (35.7)	137 (15.9)	2.94 (1.56–5.40)	<.001
Vancomycin	18 (32.1)	95 (11.0)	3.83 (1.97–7.19)	<.001
Microbiologic characteristic				
Healthcare acquired	38 (67.9)	408 (47.3)	2.35 (1.29–4.45)	.003
Urine isolate	29 (51.8)	521 (60.4)	0.71 (0.40–1.26)	.20
Blood isolate	5 (8.9)	157 (18.2)	0.44 (0.14–1.12)	.08
Respiratory isolate	13 (23.2)	98 (11.4)	2.36 (1.12–4.66)	.008

NOTE. Data are no. (%) of participants, unless otherwise indicated. Only factors with $P \leq .20$ are shown. These variables were considered for inclusion in multivariable analysis. APR-DRG, All Patient Refined Diagnosis Related Group; CI, confidence interval; ICU, intensive care unit; IQR, interquartile range; OR, odds ratio.

[a] The Fisher exact test was used for categorical variables, and the Wilcoxon rank-sum test was used for continuous variables.

[b] Transferred from another medical facility, including long-term care facilities.

[c] Amoxicillin-clavulanate, ampicillin-sulbactam, piperacillin-tazobactam, meropenem, metronidazole, and clindamycin.

TABLE 2

Multivariable Analysis (Case-Control Study)

Variable	AOR (95% CI)	*P*
APR-DRG severity of illness extreme	4.31 (2.25–8.25)	<.001
Prior fluoroquinolone use	3.39 (1.50–7.66)	.003
Prior extended-spectrum cephalosporin use	2.55 (1.18–5.52)	.02
Blood isolate	0.33 (0.12–0.86)	.02

NOTE. AOR, adjusted odds ratio; APR-DRG, All Patient Refined Diagnosis Related Group; CI, confidence interval.